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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chloroform. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA-440/4-80-033. NTIS PB 81-117442.

U.S. EPA. 1982. Hazard Profile for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Chloroform. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response.

U.S. EPA. 1985. Health Assessment Document for Chloroform. Office of Health and Environmental Assessment, Environmental Criteria Assessment Office, Research Triangle Park, NC. EPA 600/8-84/004F. NTIS PB 86-105004.

U.S. EPA. 1987a. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for chloroform. On-Line: (Verification date 12/02/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1987b. Integrated Risk Information System (IRIS). Risk estimate for carcinogenicity for chloroform. On Line: Input pending. (Verification Date 8/26/87). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived nor were larger uncertainty factors employed when the variable data were limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Chloroform has been shown to be carcinogenic by the oral route in rodents in several independent investigations. Human data are suggestive for chlorinated drinking water, but are inadequate for chloroform alone. Chloroform is classified as an EPA Group B2 carcinogen, probable human carcinogen, based on sufficient evidence from animal studies and inadequate evidence from human studies.

U.S. EPA (1985) has estimated a unit risk for inhalation exposure of 2.3×10^{-5} $(\mu g/m^3)^{-1}$ based upon route extrapolation from a q_1^* of 8.1×10^{-2} $(mg/kg/day)^{-1}$. This assessment is based upon data for incidence of liver tumors in male and female mice (NCI, 1976).

U.S. EPA (1987b) has estimated an oral q_1^* of 6.1×10^{-3} $(mg/kg/day)^{-1}$ based upon kidney tumors in male rats exposed in the drinking water in a study by Jorgenson et al. (1985).

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ATP	Adenosine triphosphate
bw	Body weight
CAS	Chemical abstract service
CS	Composite score
DENA	Diethyl nitrosamine
DNA	Deoxyribonucleic acid
GGTase	Gamma glutamyl transpeptidase
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chloroform (CAS No. 67-66-3) are as follows:

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	119.38 (Callahan et al., 1979)
Vapor pressure:	150.5 mm Hg at 20°C (Callahan et al., 1979)
Water solubility:	8200 mg/ℓ at 20°C (Callahan et al., 1979)
K_{ow}:	93 (Callahan et al., 1979)
K_{oc}:	0-40 (Hutzler et al., 1983)
Bioconcentration factor: (in bluegill, Lepomis macrochirus)	6 (Barrows et al., 1978)
Half-lives in air:	70-79 days (Atkinson, 1985; NLM, 1987)
water:	0.3-3 days in rivers 3-30 days in lakes (Zoeteman et al., 1980)

Volatilization is the primary fate process for chloroform in water because of the relatively high vapor pressure (NLM, 1987). Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms will not be significant (NLM, 1987).

The half-life of chloroform in soil could not be located in the literature searched; however, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporation half-life from water. This compound is highly mobile in most soils, especially those with high organic carbon content, (Hutzler et al., 1983) and in subsurface soil it is expected to

remain stable enough to leach into groundwater (NLM, 1987). Upon contamination of groundwater, chloroform is likely to persist for long periods of time (no degradation was observed when incubated with aquifer material for 27 weeks) (Wilson et al., 1983).

In the atmosphere, reaction with photochemically generated hydroxyl radicals will be the predominant removal mechanism (NLM, 1987). Based on a tropospheric to stratospheric turnover time of 30 years and a half-life of 70-79 days, <1% of the tropospheric chloroform is expected to diffuse into the stratosphere (Callahan et al., 1979; Atkinson, 1985; NLM, 1987). Chloroform is expected to be transported long distances from its emission sources based on the relatively slow rate of degradation in air.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Evidence from human assays (Fry et al., 1972), as well as from animal experiments (Brown et al., 1974; Taylor et al., 1974), indicates that ingested chloroform is absorbed nearly completely from the gastrointestinal tract. Brown et al. (1974) orally administered a 60 mg/kg dose of ^{14}C-chloroform to mice, rats and squirrel monkeys and recovered 93-98% of the administered dose of radioactivity in the expired air, urine and carcass 48 hours after treatment. That gastrointestinal absorption was rapid as well as extensive was further indicated by the observation that peak blood levels of radioactivity occurred at 1 hour in the mice and monkeys. In man, peak levels of ^{14}C in the blood occurred 1 hour after an oral 500 mg dose of ^{14}C-chloroform in olive oil by gelatin capsule (Fry et al., 1972).

Withey et al. (1982) administered a 75 mg/kg dose of chloroform in ~4 mL of water or corn oil to mature fasted rats to investigate the effect of vehicle on gastrointestinal absorption. The times to initial peak blood concentrations were nearly equivalent at 5.6 minutes for water and 6.0 minutes for corn oil. A second peak in blood concentration occurred at 40 minutes for corn oil-treated rats. The postabsorption peak blood concentration was 39.3 µg/mL when administered in water and 5.9 µg/mL when administered in corn oil, and the area under the blood concentration curves was 8.7 times greater for water than for corn oil, which suggests that the large volume (for a rat) of corn oil substantially slowed gastrointestinal absorption.

2.2. INHALATION

Without providing documentation, U.S. EPA (1980a) stated that 49-77% of the chloroform present in inspired air is absorbed by the respiratory tract, presumably in humans.

U.S. EPA (1985) reviewed pulmonary retention data from humans during the use of chloroform as an anesthetic (Lehmann and Hasegawa, 1910; Smith et al., 1973). Pulmonary retention, estimated by measuring the difference between inhaled and exhaled concentrations of chloroform and by measuring respiratory rate, was observed to decrease as duration of exposure increased. U.S. EPA (1985) estimated retention at equilibrium at ~65-67%. It was predicted that the percent retained would be independent of the inspired concentration and therefore that estimations based on very high concentrations used in anesthesia (~8000-10,000 ppm) would be equally applicable to the much lower levels anticipated with environmental exposure. U.S. EPA (1985) noted that chloroform retention would be expected to be higher in individuals with larger than average proportions of body fat because of the lipophilic nature of the compound.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

Table 3-1 presents a summary of the effects of subchronic chloroform exposure.

3.1.1. Oral. DeSalva et al. (1975) reported that chloroform at dose levels of 1.0 and 2.5 mg/kg/day for 1 year produced no effects on the functioning of the human liver and kidney.

No effects in rats were reported at dose levels of 15 and 30 mg/kg/day (Palmer et al., 1979); however, increased relative liver and kidney weight was observed at 150 mg/kg/day, and severe toxic effects, such as necrosis of the liver and dysfunction of the gonads were produced at 410 mg/kg/day (Palmer et al., 1979).

In an experiment to investigate the effect of vehicle on the hepatotoxicity of chloroform in mice, Bull et al. (1986) administered chloroform in corn oil or 2% Emulphor to groups of 9-10 male and 9-10 female B6C3F1 mice at 0, 60, 130 or 270 mg/kg/day for 91-94 consecutive days. In male mice, chloroform increased liver weights when given in corn oil but not when given in Emulphor. Chloroform in either vehicle increased the liver weights of female mice, but the effect was greater with corn oil. Elevated SGOT occurred in a dose-related manner in both sexes, but only when the vehicle was corn oil. Upon histopathologic examination, fatty degeneration was observed in chloroform-treated groups with the corn oil vehicle. At 270 mg/kg/day, the hepatic architecture was disrupted severely and early cirrhosis was evident. These lesions were not observed in corn oil controls or in mice treated with chloroform in Emulphor. Minimal to mild focal necrosis was the only lesion observed in mice treated with chloroform in Emulphor.

TABLE 3-1

Subchronic Toxicity of Chloroform

Route	Dose or Exposure	Duration of Treatment	Species/Strain	Sex	Number Treated	Effect	Reference
Inhalation	0 ppm 25 ppm (122 mg/m³) 50 ppm (244 mg/m³) 85 ppm (415 mg/m³) 25 ppm (122 mg/m³)	7 hours/day, 5 days/week for 6 months 4 hours/day, 5 days/week	rats/NR	M/F M/F M/F M/F M/F	10-12 10-12 10-12 10-12 10	Exposure to chloroform at 25 ppm for 4 hours/day had no effect on male rats; at 25 ppm for 7 hours/day, histopathologic changes in the liver were present in males but not females; at higher doses, increasingly pronounced changes were present in the liver and kidneys of both sexes.	Torkelson et al., 1976
Inhalation	0 ppm 25 ppm (122 mg/m³) 50 ppm (244 mg/m³) 85 ppm (415 mg/m³)	7 hours/day, 5 days/week up to 203 days	guinea pigs/NR	M/F M/F M/F M/F	16-24 16-24 16-24 16-24	Pneumonitis was seen in females exposed to 85 ppm, and histopathological changes were observed in the livers and kidneys of both sexes exposed to 25 ppm but not 50 ppm.	Torkelson et al., 1976
Inhalation	0 ppm 25 ppm (122 mg/m³) 50 ppm (244 mg/m³) 85 ppm (415 mg/m³)	7 hours/day, 5 days/week up to 203 days	rabbits/NR	M/F M/F M/F M/F	4-6 4-6 4-6 4-6	Hepatic and renal pathology was seen in females exposed to 85 ppm, and pneumonitis and hepatic necrosis in males exposed to 85 ppm. Histopathological changes were observed in the livers and kidneys of both sexes exposed to 25 ppm but not 50 ppm.	Torkelson et al., 1976
Oral	0 1.0 mg/kg/day 2.5 mg/kg/day	1 year	human	NR	NR	Liver and kidney function tests indicated that there were no statistically significant differences between chloroform-treated individuals and controls.	DeSalva et al., 1975
Oral	0 15 mg/kg/day 30 mg/kg/day 150 mg/kg/day 410 mg/kg/day	13 weeks	rats/ Sprague-Dawley	M/F	20 20 20 20 20	Increased liver weight with fatty necrosis, gonadal atrophy and cellular proliferation in the bone marrow occurred at 410 and 150 mg/kg/day. No effects were reported for dose levels of 30 and 15 mg/kg/day.	Palmer et al., 1979

NR = Not reported

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The investigators concluded that the vehicle strongly influences the hepatotoxicity of chloroform in mice and that the difference in vehicle may explain the markedly different results observed in cancer studies in mice when nearly equivalent total doses were given in corn oil (NCI, 1976) or drinking water (Jorgenson et al., 1985) (Chapter 4).

3.1.2. Inhalation. Torkelson et al. (1976) exposed rats, guinea pigs and rabbits to 25, 50 or 85 ppm (122, 244 or 415 mg/m³, respectively), 7 hours/day, 5 days/week for 6 months (see Table 3-1). Exposure to 25 ppm chloroform produced histopathological changes in the livers and kidneys of male but not female rats. At higher doses, lobular granular degeneration and focal necrosis were increased in the liver, and cloudy swelling of epithelial cells was increased in the kidney. These changes were reported to be reversible after 6 weeks. Hematological, clinical chemistry and urinalysis values were "within normal limits." The results obtained from chloroform exposure in guinea pigs and rabbits are difficult to interpret because adverse effects were seen at the low-dose (25 ppm) and high-dose (85 ppm) levels, but no effects were reported at the intermediate-dose level (50 ppm).

3.2. CHRONIC

3.2.1. Oral. Several chronic oral studies (NCI, 1976; Palmer et al., 1979; Roe et al., 1979) were designed to test the carcinogenicity of chloroform (Chapter 4). Depression of body weight was observed at chloroform doses $\geq$60 mg/kg/day in rats (NCI, 1976; Palmer et al., 1979) and mice (Roe et al., 1979). Palmer et al. (1979) exposed Sprague-Dawley rats of both sexes to 60 mg/kg/day of chloroform in a toothpaste base for 80 weeks followed by 15 weeks of observation. Decreased relative liver weight and plasma cholinesterase levels were reported in female rats (Palmer et al., 1979). Rats of both sexes survived better than the controls, though both

groups had a high incidence of non-neoplastic respiratory and renal disease. There were no treatment-related effects on the incidence of liver or kidney tumors following treatment of 60 mg/kg/day for 80 weeks. Although histologically - malignant mammary tumors were reported more in treated than in control female rats, the difference was not statistically significant (Palmer et al., 1979). Higher chloroform doses (90 and 180 mg/kg/day, 5 days/week for 78 weeks) resulted in an increased incidence of noncancerous respiratory diseases in rats (NCI, 1976), and a gavage dose of 477 mg/kg/day for 78 weeks resulted in decreased survival in female mice (NCI, 1976).

Heywood et al. (1979) administered chloroform in a toothpaste base in gelatin capsules at 15 or 30 mg/kg/day, 6 days/week for 7.5 years to groups of eight male and eight female beagle dogs. A control group of 16 dogs/sex was maintained. Fatty cysts developed in the livers of some dogs in each of the treated groups, and was considered to be treatment-related. SGPT and other serum enzyme indicators of liver damage were elevated in a dose-related fashion.

Chronic exposure of humans to chloroform appears to result in adverse effects on the central nervous system (NIOSH, 1974), although there are no data on the dose relation of the effects. In addition, chloroform affects the liver and kidneys in humans (NIOSH, 1974). The potential for chronic human oral exposure to chloroform has increased because of the widespread practice of chlorinating drinking water (U.S. EPA, 1980a).

3.2.2. Inhalation. Epidemiological studies of humans exposed to chloroform in the workplace at levels ranging from 22-237 ppm have indicated that tiredness, depression, gastrointestinal disturbances (e.g., flatulence, nausea), headache and frequent and scalding urination are the primary symptoms (Challen et al., 1958; Bomski et al. 1967). Regarding long-term effects, Challen et al. (1958) reported that there was no evidence of

organic lesions attributable to chloroform, based on physical exams and liver function tests. Bomski et al. (1967) reported that chloroform exposure at levels as low as 2 ppm for 1-4 years may result in an increased incidence of toxic hepatitis, splenomegaly and hepatomegaly, although no statistical analysis and adequate controls were presented.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Thompson et al. (1974) performed oral range-finding and developmental toxicity studies where Sprague-Dawley rats and Dutch-Belted rabbits were used. In the range-finding study, groups of six rats were treated by gavage with 79, 126, 300, 316 or 516 mg/kg/day of chloroform in corn oil on days 6-15 of gestation. Maternal toxicity was observed at $\geq$126 mg/kg/day and fetotoxicity was observed at $\geq$316 mg/kg/day. In the definitive study, groups of 25 rats were treated with 20, 50 or 126 mg/kg/day. Maternal toxicity was observed at $\geq$50 mg/kg/day, but no adverse developmental effects were reported at any level. The range-finding study used groups of five rabbits and doses of 25, 63, 100, 159, 251 or 398 mg/kg/day on days 6-18 of gestation; maternal toxicity was observed at all dosage levels. In the two dams that survived at 100 mg/kg/day one had four resorptions and the other was not pregnant. The definitive rabbit study was performed with groups of 15 rabbits treated with at 20, 35 and 50 mg/kg/day. Reduced maternal body weight was observed at 35 but not at 50 mg/kg/day and reduced fetal body weight was observed at 35 but not at 20 or 50 mg/kg/day.

Ruddick et al. (1983) administered chloroform at 100, 200 or 400 mg/kg/day to groups of 15 mated Sprague-Dawley rats on days 6-15 of gestation. A dose-related decrease in maternal body weight gain was observed at all dosage levels, while fetal body weight was decreased only at 400 mg/kg/day.

This group also had a higher incidence of sternebral anomalies and fetal runts.

Palmer et al (1979) performed a study in which Sprague-Dawley rats were given daily gavage doses of 0, 15, 30, 150 and 410 mg/kg/day of chloroform in toothpaste (10 of each sex per dose level) for 13 weeks and observed gonadal atrophy in both sexes treated with 410 mg/kg/day.

Burkhalter and Balster (1979) investigated the effects of chloroform at 31.1 mg/kg/day on behavior in developing ICR mice. Mice were treated from 21 days before mating until 21 days after birth. The offspring were treated on days 7-21 of age. Treatment had no effect on litter size, but offspring body weights were reduced. There was no definite effect of treatment on the behavior of the offspring.

3.3.2. Inhalation. Schwetz et al. (1974) exposed groups of 20 female Sprague-Dawley rats to chloroform at 30, 100 or 300 ppm (146, 488 or 1465 mg/m^3), 7 hours/day on gestation days 6-15. Maternal toxicity, manifested as decreased maternal weight gain, occurred in all exposed groups. Reduced fetal crown-rump length was observed at 30 and 300 ppm but not at 100 ppm. Severe teratogenic effects were observed at $\geq$100 ppm. Fetal resorption was greatly increased at 300 ppm. Murray et al. (1979) exposed groups of mated CF-1 mice to chloroform at 100 ppm, 7 hours/day on days 6-15 of gestation. Other groups of mice were exposed to 100 ppm, 7 hours/day on days 1-7 or 8-15 of gestation. Effects reported during one or more of the three periods of exposure include increased resorptions/litter, decreased fetal body weight and crown-rump length, delayed skeletal ossification, increased incidence of cleft palate and maternal toxicity manifested as reduced rate of body weight gain and increased liver weight.

3.4. TOXICANT INTERACTIONS

The toxicity of chloroform is greatly influenced by anything that alters microsomal enzyme activity or hepatic GSH levels (U.S. EPA, 1985). The substances that potentiate the toxic effects of chloroform are methyl n-butyl ketone (Branchflower and Pohl, 1981), alcohol (Kutob and Plaa, 1961), carbon tetrachloride (Harris et al., 1982), chlordecone (Iijima et al., 1983), DDT and phenobarbital (McLean, 1970). Methyl n-butyl ketone increases the toxicity of chloroform by lowering glutathione levels and by increasing the levels of hepatic cytochrome P-450 (which, in turn, increases the metabolism of chloroform to phosgene) and by decreasing GSH levels (Branchflower and Pohl, 1981). Harris et al. (1982) reported that carbon tetrachloride potentiated the toxic effects of chloroform because of increased phosgene formation and the initiation of lipid peroxidation. The mechanism of interaction for alcohol, chlordecone, DDT and phenobarbital was not discussed. von Oettingen (1964) reported that high-fat/low-protein diets potentiated the hepatotoxic effects of chloroform in animals.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Although chloroform has not unequivocally been shown to cause human cancer, ecological and case control studies (Alavanja et al., 1978; Cantor et al., 1978; Brenniman et al., 1978; Hogan et al., 1979; Struba, 1979; Gottlieb et al., 1981; Young et al., 1981) have consistently supported the association of increased risk of bladder, colon and rectal cancer with oral exposure to chlorinated drinking water (U.S. EPA, 1983) in which trihalomethanes and chloroform are the contaminants present in greatest quantities. A detailed description of these studies and their strengths and weaknesses is available in U.S. EPA (1985).

4.1.2. Inhalation. Pertinent data regarding an association between chloroform inhalation and an increased incidence or risk of cancer were not located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Table 4-1 summarizes the available data from several early gavage bioassays of chloroform carcinogenicity. Eschenbrenner and Miller (1945) reported that a dose level of chloroform that caused hepatic necrosis when given once would cause hepatic carcinoma when given repeatedly. The NCI (1976) found a dose-related increase in hepatomas in both sexes when mice received chloroform in corn oil by gavage, and an increase in renal epithelial tumors in male rats receiving chloroform in corn oil by gavage (see Table 4-1). The increased incidence of hepatic and renal tumors was statistically significant ($p<0.05$). Palmer et al. (1979) criticized the NCI (1976) study because rats being treated with other volatile carcinogenic substances were housed in the same room as the chloroform-treated rats.

TABLE 4-1

Oral Bioassays of Chloroform Carcinogenicity

Vehicle	Dose	Duration of Treatment	Duration of Study (weeks)	Species/Strain	Sex	Number Treated	Target	Effects	Reference
Olive oil	150 mg/kg bw 300 mg/kg bw 600 mg/kg bw 1200 mg/kg bw 2400 mg/kg bw	once every 4 days for a total of 30 doses	NR	mice/ (strain A)	NR	NR	liver	Doses of 150 and 300 mg/kg bw produced neither necrosis nor carcinoma in the liver. Doses of 600-2400 mg/kg bw produced necrosis when given once, and hepatomas when given repeatedly. All females at the highest dose and all males at the three highest doses died early in the experiment.	Eschenbrenner and Miller, 1945
Corn oil	0 mg/kg/day 138 mg/kg/day 277 mg/kg/day 238 mg/kg/day 477 mg/kg/day 0 mg/kg/day	5 days/week for 78 weeks	92-93	mice/B6C3F1	M M M F F F	18 50 45 45 41 20	liver	Hepatocellular carcinomas were found in 1/18 (6%) control males, 18/50 (36%) low-dose males and 44/45 (98%) high-dose males; in 0/20 control females, 36/45 (80%) low-dose females and 39/41 (95%) high-dose females.	NCI, 1976
Corn oil	0 mg/kg/day 90 mg/kg/day 180 mg/kg/day 100 mg/kg/day[a] 200 mg/kg/day[a] 0 mg/kg/day	5 days/week for 78 weeks	111	rats/ Osborne-Mendel	M M M F F F	19 50 50 49 48 20	kidney	Renal carcinomas and adenomas were found in 0/19 control males, 4/50 (8%) low-dose males and 12/50 (24%) high-dose males; 0/20 control females, 0/49 low-dose females and 2/48 (4%) high-dose females. Thyroid tumors were found in 1/20 control females, 8/49 low-dose females and 10/48 high-dose females.	NCI, 1976
Toothpaste[b]	0 mg/kg/day 15 mg/kg/day 75 mg/kg/day 165 mg/kg/day	6 days/week for 52 weeks	52	rats/ Sprague-Dawley	M M M M	75 25 25 25	none	No treatment-related neoplastic effects were seen in comparison with controls; however, all groups had a high incidence of pulmonary and renal histopathology.	Palmer et al., 1979
Toothpaste[b]	0 mg/kg/day 15 mg/kg/day 75 mg/kg/day 165 mg/kg/day	6 days/week for 52 weeks	52	rats/ Sprague-Dawley	F F F F	75 25 25 25	none	Same as above	Palmer et al., 1979

Because chloroform has been a contaminant in toothpaste, rats (Palmer et al., 1979), mice (Roe et al., 1979) and dogs (Heywood et al, 1979) were treated with chloroform in a toothpaste base including essential oils as flavor components. Range-finding studies were performed in all experiments. No effects at dose levels of 15, 75 and 165 mg/kg/day for 52 weeks were reported in rats. When female rats were treated with 60 mg/kg/day for 96 weeks, however, there was an increase ($p=0.056$) in malignant mammary gland tumors in the chloroform-treated group, although the untreated group developed benign mammary tumors (Palmer et al., 1979). There was an increased incidence of kidney tumors in the high-dose (60 mg/kg/day) level in male mice (Roe et al., 1979). The females had no increased incidence of cancer, but there appeared to be some confounding influence because of the vehicle. The authors addressed, but did not resolve, the problem of the effect produced by different vehicles (Roe et al., 1979).

Recent studies indicate that chloroform is carcinogenic to rats and mice when administered in drinking water. Tumasonis et al. (1985) provided groups of 32 male and 45 female Wistar rats with drinking water containing chloroform for lifetime. The initial concentration, 2.9 g/ℓ (2900 ppm), was reduced by one-half after 72 weeks to maintain a fairly constant intake of chloroform because water consumption had increased. The dosage of chloroform is estimated at ~200 mg/kg/day for both sexes, based on graphic data provided by the investigators. Controls consisted of 28 male and 22 female rats provided with tap water. Treated rats weighed substantially less than their sex-matched controls throughout the experiment. Survival appeared not to be affected by treatment. The most noteworthy observation was a significantly increased incidence of neoplastic nodules in the liver of female rats, 10/40 compared with 0/18 in controls ($p<0.03$).

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Jorgenson et al. (1985) provided drinking water containing chloroform at 0, 200, 400, 900 or 1800 mg/ℓ (ppm) to groups of male Osborne-Mendel rats and female B6C3F1 mice for 104 weeks. Because water consumption is reduced with high concentrations of chloroform, a matched control group was provided water in amount to match the consumption of the high-dose groups. For rats, group sizes were 330 for controls and 200 ppm, 150 at 400 ppm and 50 for matched controls, 900 and 1800 ppm. Group sizes for mice were identical to rats, except that the control and 200 ppm groups contained 430 mice. Survival of mice appeared to be unaffected by treatment. Treated rats survived longer than controls, attributed by the investigators to the fact that treated animals were leaner because of decreased water and food intake. Several tumor types occurred in rats at a significantly increased incidence, but only kidney tumors, which occurred in a dose-related manner, were attributed to treatment with chloroform. The incidence of kidney tumors in the rats is presented in Table 4-2. No tumor type occurred in female mice at a significantly greater incidence in treated groups than in controls.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled chloroform were not located in the available literature.

4.3. OTHER RELEVANT DATA

Chloroform was not mutagenic in Escherichia coli strains K12, WP2p and WP2uvrA⁻p or in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 (Kirkland et al., 1981) with or without S-9 metabolic activation. Chloroform was not mutagenic in cultured Chinese hamster lung fibroblasts at the 8-azaguanine locus (Sturrock, 1977), nor did chloroform increase sister chromatid exchanges in cultured Chinese hamster ovary cells or human lymphocytes (White et al., 1979; Uehleke et al., 1977). In a recent experiment in

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TABLE 4-2

Kidney Tumors in Male Osborne-Mendel Rats Exposed to Chloroform in Drinking Water for 104 Weeks[a]

Tumor Type	Control	Matched Control	Chloroform Concentration (ppm)				Overall p Value[b]
			200	400	900	1800	
Tubular cell adenoma	4/301[c] (1)	0/50 (0)	2/313 (1)	3/148 (2)	2/48 (4)	5/50[d] (10)	<0.0001
Tubular cell adenoma and adenocarcinoma	4/301 (1)	1/50 (2)	4/313 (1)	4/148 (3)	3/48 (6)	7/50[d] (14)	<0.0001
All kidney tumors	5/301 (2)	1/50 (2)	6/313 (2)	7/148 (5)	3/48 (6)	7/50[d] (14)	<0.0001

[a]Source: Jorgenson et al., 1985

[b]Overall p value calculated using Peto trend test, corrected for continuity and survival.

[c]Incidence values are numbers of rats with tumors/effective number of rats at risk (continuity corrected); values in parentheses are percentages of rats with indicated tumor.

[d]Individual treatment group statistically different from control group at $p<0.01$.

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which chloroform was used at a higher concentration, chloroform induced sister chromatid exchange in cultivated human lymphocytes (Morimoto and Koizumi, 1983). Chloroform was reported to be weakly positive or "suggestive" in mutagenicity assays in Saccharomyces cerevisiae D7 in the presence of S-9 metabolic activation, and in the induction of murine sperm head abnormalities (Agustin and Lim-Sylianco, 1978; Callen et al., 1980; Land et al., 1981; Topham, 1980; Gocke et al., 1981).

Several authors have investigated the mechanism for chloroform-induced carcinogenicity in laboratory animals. Reitz et al. (1982) measured DNA alkylation and repair and cellular regeneration in male B6C3F1 mice given single 15, 60 or 240 mg/kg oral doses of chloroform. DNA alkylation, estimated as μmol of bound chloroform/mol of DNA, was 1.5, compared with 6000-7430 μmol/mol for dimethylnitrosamine, a known genotoxic carcinogen. Using a technique involving incorporation of ^{3}H-thymidine into DNA following treatment with hydroxyurea sufficient to depress normal DNA synthesis, these investigators determined that chloroform did not induce DNA repair in the livers of treated rice. Cellular regeneration, estimated by ^{3}H-thymidine incorporation into DNA in nonhydroxyurea-treated mice, was increased 14-fold in the liver and 25-fold in the kidneys of chloroform-treated mice. The authors concluded that carcinogenicity associated with chloroform was due to cellular necrosis rather than to DNA damage.

In initiation-promotion experiments with male Sprague-Dawley rats, Pereira et al. (1982) determined that chloroform did not initiate the development of GGTase-positive foci in the livers of rats promoted with phenobarbital, and the results concerning the promoting activity in rats pretreated with diethylnitrosamine (DENA), was not conclusive. Deml and

Oesterle (1985), however, reported that chloroform promoted the development of DENA-induced ATPase deficient foci and GGTase-positive foci in the livers of female Sprague-Dawley rats.

Klaunig et al. (1986) provided chloroform in drinking water for 52 weeks to male B6C3F1 mice that were treated with DENA in drinking water for 4 weeks to initiate tumor formation. Neither DENA nor chloroform alone increased the incidence of tumors, but chloroform inhibited liver and lung tumorigenesis in the DENA-initiated mice.

4.4. WEIGHT OF EVIDENCE

Oral exposure to chloroform has caused hepatic carcinomas in male and female B6C3F1 mice (NCI, 1976), renal carcinomas and adenomas in male Osborne-Mendel rats (NCI, 1976; Jorgenson et al., 1985) and in male ICI mice (Roe et al., 1979), thyroid tumors in female Osborne-Mendel rats (NCI, 1976) and an slightly increased incidence of malignant mammary gland tumors after chronic exposure in Sprague-Dawley rats (Palmer et al., 1979). Evidence is sufficient to classify chloroform as an animal carcinogen. Although some association between oral exposure to chlorinated drinking water (in which trihalomethanes and chloroform usually predominates) and human bladder, intestinal and rectal cancer has been reported (see Section 4.1.1.), the evidence for human carcinogenicity of chloroform itself is inadequate. Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans adopted by the Carcinogen Assessment Group of the U.S. EPA (1986), chloroform is classified in Group B2, a probable human carcinogen. This classification is consistent with the analysis by U.S. EPA (1985).

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1986a,b) recommends a TWA-TLV of 10 ppm (50 mg/m³) for occupational exposure to chloroform and also notes that chloroform has induced cancer in animals by the oral route at high and intermediate dose levels and is a suspected carcinogen for humans. OSHA (1985) has set a ceiling limit for chloroform of 50 ppm (240 mg/m³) in the workroom atmosphere.

U.S. EPA (1987a) reports an RfD for oral exposure to chloroform of $1x10^{-2}$ mg/kg/day or 1 mg/day for a 70 kg human, based on the development of fatty cysts in the livers of dogs treated with 15 mg/kg/day, 6 days/week for 7.5 years (Heywood et al., 1979).

The Carcinogen Assessment Group (U.S. EPA, 1985) analyzed the following data: liver tumors in female mice (NCI, 1976); liver tumors in male mice (NCI, 1976); kidney tumors in male rats (NCI, 1976; Jorgenson et al., 1985); and kidney tumors in male mice (Roe et al., 1979). The largest estimates of carcinogenic potency were derived from the liver tumor data in male and female mice in the NCI (1976) gavage study. A q_1^* of $8.1x10^{-2}$ $(mg/kg/day)^{-1}$ was derived as the geometric mean of the q_1^*s derived separately for male and female mice. A complete discussion of this derivation is presented in U.S. EPA (1985). More recently, the CRAVE work group (U.S. EPA, 1987b) recommended that the q_1^* for oral exposure via drinking water be based upon the drinking water study by Jorgenson et al. (1985). The Jorgenson study was included in the Health Assessment Document for Chloroform (U.S. EPAS, 1985) but was not selected as the primary basis for drinking water risk estimation. Given the CRAVE action (U.S. EPA, 1987b), the Agency now uses the q_1^* value of $6.1x10^{-3}$ $(mg/kg/day)^{-1}$ based on

the incidence of kidney tumors in male rats in the study by Jorgenson et al. (1985). The upper bound estimate of cancer risk for exposure to 1 µg/L of chloroform in water is 1.7×10^{-7}.

Using q_1^* of 8.1×10^{-2} $(mg/kg/day)^{-1}$, EPA (1985) calculated upper-bound estimates of cancer risk for exposure to 1 µg/m³ in air to be 2.3×10^{-5}. This q_1^* for inhalation exposure to chloroform was validated by the CRAVE work group on August 26, 1987 (EPA, 1987).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Chloroform is known to be carcinogenic to animals and is suspected of being carcinogenic to humans. Data are sufficient for derivation of a q_1^*; therefore, it is inappropriate to derive an RfD_S for this chemical.

6.2. REFERENCE DOSE (RfD)

Chloroform is known to be carcinogenic to animals and is suspected of being carcinogenic to humans. Data are sufficient for derivation of a q_1^*; therefore, it is inappropriate to derive an RfD for this chemical.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The CRAVE work group (EPA, 1987) validated a q_1^* of 6.1×10^{-3} $(mg/kg/day)^{-1}$ based on the incidence of kidney tumors in male rats exposed in drinking water in the study by Jorgenson et al. (1985). The upper bound estimate of cancer risk for exposure to 1 µg/L of chloroform in water is 1.7×10^{-7}.

In this reevaluation, it was concluded that oral exposure in the drinking water approximated potential human exposure more appropriately than did gavage exposure using an oil vehicle. For this reason, the Jorgenson et al. (1985) study was selected as the basis for potency estimation as compared to a previous estimate which utilized data from NCI (1976) as the basis.

6.3.2. Inhalation. Data regarding the carcinogenicity of inhaled chloroform in humans and animals were not available. Studies in animals indicate that chloroform is carcinogenic by the oral route. NCI (1976) found dose-related increased incidences of hepatocellular carcinoma in male and female mice treated by gavage at time-weighted average (TWA) doses of $\geq$138 mg/kg/day 5 days/week for 78 weeks, and a dose-related increased incidence of kidney epithelial tumors in male rats similarly treated by

gavage at 90 and 180 mg/kg/day. Roe et al. (1979) found an increased incidence of kidney epithelial tumors in male mice given 60 mg/kg/day 6 days/week for 78 weeks. Dose-related increased incidences of renal tubular cell adenomas and/or carcinomas were found in male rats treated with chloroform in the drinking water at levels equivalent to dosages ≥38 mg/kg/day for 104 weeks (Jorgenson et al., 1985).

The U.S. EPA (1985a) considered these five data sets in determining the q_1^* for chloroform. The five data sets were as follows: 1) liver tumors in female mice (NCI, 1976), 2) liver tumors in male mice (NCI, 1976), 3) kidney tumors in male rats (NCI, 1976), 4) kidney tumors in male mice (Roe et al., 1979), and 5) kidney tumors in male rats (Jorgenson et al., 1985). U.S. EPA (1985a) used available pharmacokinetic data to calculate an effective dose for these studies, assuming that the amount metabolized to reactive metabolites is the gavage dose minus the amount excreted unchanged. For mice given 60 mg/kg, as in the Roe et al. (1979) study, the correction was 6%. For rats at the same dosage, it was 20%. In the NCI (1976) study in which rats and mice received doses of ~200-500 mg/kg/day, a 20% correction was considered conservative and would probably overestimate the amount metabolized from these doses. U.S. EPA (1985a) used these correction factors to reduce the administered dose by the unmetabolized portion (6% in mice and 20% in rats when given as a bolus by gavage in corn oil, 0% when administered in drinking water). Doses were also corrected for differences between animal and human pharmacokinetics by using a surface area correction. Using these corrected doses, maximum likelihood estimates of the parameters of the multistage model were calculated for each of the five data sets. U.S. EPA (1985a) chose the mouse liver tumor data from the NCI (1976) study as the basis of the potency factor for inhalation exposure

to chloroform. The NCI (1976) study is considered to be appropriate for use in the inhalation risk estimate because there were no inhalation cancer bioassays and no pharmacokinetic data to contraindicate the use of gavage data (U.S. EPA, 1987b). The geometric mean of the estimates for male and female mice in the NCI (1976) study, 8.1×10^{-2} $(mg/kg/day)^{-1}$, was recommended as the inhalation q_1^* for chloroform. U.S. EPA (1985a) combined the estimates for both data sets because the data for males included observations at a lower dose, which appeared to be consistent with the female data. U.S. EPA (1985a) noted that the recommended q_1^* was similar to the geometric mean calculated from all five estimates and was also similar to the estimate calculated if data for both sexes of B6C3F1 mice in the NCI (1976) study were pooled. Using q_1^* of 8.1×10^{-2} $(mg/kg/day)^{-1}$, U.S. EPA (1985) calculated upper-bound estimates of cancer risk for exposure to 1 $\mu g/m^3$ in air to be 2.3×10^{-5}. This q_1^* for inhalation exposure to chloroform was validated by the CRAVE work group on August 26, 1987 (U.S. EPA, 1987b).

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APPENDIX

Summary Table for Chloroform

Route	Species	Experimental Dose/Exposure	Effect	q_1^* or Unit Risk	Reference
Inhalation	mouse	138-477 mg/kg/ corn oil gavage	hepatocellular carcinoma	2.3×10^{-5}† $(\mu g/m^3)^{-1}$	NCI, 1976; U.S. EPA, 1985
Oral	rat	200-1800 mg/ℓ/ drinking water	kidney tumors	6.1×10^{-3} $(mg/kg/day)^{-1}$	Jorgenson et al., 1985; U.S. EPA, 1987b

†Based on a q_1^* of 8.1×10^{-2} $(mg/kg/day)^{-1}$